Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	**PIs:** • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV, with or without RTV. **NRTIs:** • Lower incidence reported with TDF than with TAF. **NNRTIs:** • Lower incidence reported with NVP, RPV, and ETR than with EFV.	**Onset:** • As early as 2 weeks to months after beginning therapy **Presentation** *PIs:* • ↑ LDL-C, TC, and TG *NRTIs:* • ↑ LDL-C, TC, and TG *NNRTIs:* • ↑ LDL-C, TC, and HDL-C	Reported frequency varies with specific ARV regimen, duration of ART, and the specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% of young children receiving LPV/r will have lipid abnormalities. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Higher abnormal fasting serum lipids have been observed in ART-naive adults who received EVG/c/FTC/TAF than in those who received EVG/c/FTC/TDF. Increase in serum lipids from baseline has also been noted in adolescents receiving EVG/c/FTC/TAF.	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature ASCVD Metabolic syndrome Fat maldistribution	**Prevention:** • Low-fat diet • Exercise • Smoking-prevention counseling • When possible, use ARVs associated with a lower prevalence of dyslipidemia. These include INSTIs and newer PIs (e.g., ATV, DRV). **Monitoring**[a] *Adolescents and Adults:* • Obtain FLP (TC, HDL-C, non-HDL-C, LDL-C, and TG) twice (>2 weeks but ≤3 months apart, average these results) Monitor FLP every 6 months (for abnormal results) or every 12 months (for normal results). *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain nonfasting screening lipid profiles at entry into care and then every 6–12 months, depending on the results. • If TG or LDL-C is elevated or if a patient has additional risk factors, obtain FLP. *Children with Lipid Abnormalities and/or Additional Risk Factors:* • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:* • Obtain 12-hour FLP, LFT, and CK at 4 weeks, 8 weeks, and 3 months after starting lipid therapy.	Assess all patients for additional ASCVD risk factors. Patients with HIV are considered to be at moderate risk of ASCVD.[b] ARV regimen changes should be considered, especially when the patient is receiving older PIs (e.g., LPV/r) and/or RTV boosting. Switching to a PI-sparing regimen, a PI-based regimen with a more favorable lipid profile, or COBI boosting causes a decline in LDL-C or TG values. However, the lipid-lowering effect for LDL-C is less pronounced than with statin therapy. Refer patients to a lipid specialist early if LDL-C is ≥250 mg/dL or TG is ≥500 mg/dL. If LDL-C is ≥130 mg/dL but <250 mg, or TG is ≥150 mg/dL but <500 mg/dL, the following staged treatment approach is recommended by the NHLBI guidelines:[b] • Implement diet, nutrition, and lifestyle management for 6–9 months. Consult with a dietician if one is available. • If a 6-month to 9-month trial of lifestyle modification fails and the patient is aged ≥10 years, consider implementing lipid-lowering therapy after consulting a lipid specialist. • Statin therapy should be considered for patients with elevated LDL-C levels. NHLBI provides recommendations for statin therapy in patients with specific LDL-C levels and risk factors.[b]

Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia, continued					• If there are minimal alterations in AST, ALT, and CK, monitor every 3–4 months during the first year and every 6 months thereafter (or as clinically indicated). • Repeat FLP 4 weeks after increasing doses of antihyperlipidemic agents.	• Drug therapy can be considered in cases of severe hypertriglyceridemia (TG ≥500 mg/dL). Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used. The long-term risks of lipid abnormalities in children who are receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature ASCVD.

[a] Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and TG from nonfasting blood samples and follow up abnormal values with a test done in the fasted state.

[b] Refer to the NHLBI guidelines: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.

Key: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FLP = fasting lipid profile; FTC = emtricitabine; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides

References

1. Tassiopoulos K, Williams PL, Seage GR, 3rd, et al. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. *J Acquir Immune Defic Syndr.* 2008;47(5):607-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18209684.

2. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS.* 2009;23(6):661-672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19279441.

3. Rhoads MP, Lanigan J, Smith CJ, Lyall EG. Effect of specific ART drugs on lipid changes and the need for lipid management in children with HIV. *J Acquir Immune Defic Syndr.* 2011;57(5):404-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21499114.

4. Jacobson DL, Williams P, Tassiopoulos K, Melvin A, Hazra R, Farley J. Clinical management and follow-up of hypercholesterolemia among perinatally HIV-infected children enrolled in the PACTG 219C study. *J Acquir Immune Defic Syndr.* 2011;57(5):413-420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21602698.

5. O'Gorman CS, O'Neill MB, Conwell LS. Considering statins for cholesterol-reduction in children if lifestyle and diet changes do not improve their health: a review of the risks and benefits. *Vasc Health Risk Manag.* 2011;7:1-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21339908.

6. Singh S, Willig JH, Mugavero MJ, et al. Comparative effectiveness and toxicity of statins among HIV-infected patients. *Clin Infect Dis.* 2011;52(3):387-395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21189273.

7. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Integrated guidelines for cardiovascular health and risk reduction in children and adolescents. 2012. Available at: https://www.nhlbi.nih.gov/files/docs/peds_guidelines_sum.pdf.

8. Food and Drug Administration. FDA drug safety communication: interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm.

9. Langat A, Benki-Nugent S, Wamalwa D, et al. Lipid changes in Kenyan HIV-1-infected infants initiating highly active antiretroviral therapy by 1 year of age. *Pediatr Infect Dis J.* 2013;32(7):e298-304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23385950.

10. Casado JL, de Los Santos I, Del Palacio M, et al. Lipid-lowering effect and efficacy after switching to etravirine in HIV-infected patients with intolerance to suppressive HAART. *HIV Clin Trials.* 2013;14(1):1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23372109.

11. Lazzaretti RK, Kuhmmer R, Sprinz E, Polanczyk CA, Ribeiro JP. Dietary intervention prevents dyslipidemia associated with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected individuals: a randomized trial. *J Am Coll Cardiol.* 2012;59(11):979-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22402068.

12. Strehlau R, Coovadia A, Abrams EJ, et al. Lipid profiles in young HIV-infected children initiating and changing antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2012;60(4):369-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22134152.

13. Hazra R, Cohen RA, Gonin R, et al. Lipid levels in the second year of life among HIV-infected and HIV-exposed uninfected Latin American children. *AIDS.* 2012;26(2):235-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22008654.

14. Arpadi S, Shiau S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child.* 2013;98(4):258-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23220209.

15. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc.* 2013;16:18600. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782481.

16. Blazquez D, Ramos-Amador JT, Sainz T, et al. Lipid and glucose alterations in perinatally-acquired HIV-infected adolescents and young adults. *BMC Infect Dis.* 2015;15:119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25880777.

17. Bwakura-Dangarembizi M, Musiime V, Szubert AJ, et al. Prevalence of lipodystrophy and metabolic abnormalities in HIV-infected African children after 3 years on first-line antiretroviral therapy. *Pediatr Infect Dis J.* 2015;34(2):e23-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25068287.

18. Dejkhamron P, Unachak K, Aurpibul L, Sirisanthana V. Insulin resistance and lipid profiles in HIV-infected Thai children receiving lopinavir/ritonavir-based highly active antiretroviral therapy. *J Pediatr Endocrinol Metab.* 2014;27(5-6):403-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24259240.

19. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on antiretroviral therapy. *Pediatr Infect Dis J.* 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26421804.

20. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials. *Lancet.* 2015;385(9987):2606-2615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25890673.

21. Lee FJ, Monteiro P, Baker D, et al. Rosuvastatin vs. protease inhibitor switching for hypercholesterolaemia: a randomized trial. *HIV Med.* 2016;17(8):605-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26987376.

22. Ramteke SM, Shiau S, Foca M, et al. Patterns of growth, body composition, and lipid profiles in a South African cohort of human immunodeficiency virus-infected and uninfected children: a cross-sectional study. *J Pediatric Infect Dis Soc.* 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28481997.

23. Melvin AJ, Montepiedra G, Aaron L, et al. Safety and efficacy of atorvastatin in human immunodeficiency virus-infected children, adolescents and young adults with hyperlipidemia. *Pediatr Infect Dis J.* 2017;36(1):53-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27749649.

24. Jao J, Yu W, Patel K, et al. Improvement in lipids after switch to boosted atazanavir or darunavir in children/adolescents with perinatally acquired HIV on older protease inhibitors: results from the Pediatric HIV/AIDS Cohort Study. *HIV Med.* 2018;19(3):175-183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29159965.

25. Echecopar-Sabogal J, D'Angelo-Piaggio L, Chaname-Baca DM, Ugarte-Gil C. Association between the use of protease inhibitors in highly active antiretroviral therapy and incidence of diabetes mellitus and/or metabolic syndrome in HIV-infected patients: A systematic review and meta-analysis. *Int J STD AIDS.* 2018;29(5):443-452. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28956700.

26. Echeverria P, Bonjoch A, Puig J, Ornella A, Clotet B, Negredo E. Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia. *HIV Med.* 2017;18(10):782-786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28671337.

27. Vieira ADS, Silveira G. Effectiveness of n-3 fatty acids in the treatment of hypertriglyceridemia in HIV/AIDS patients: a meta-analysis. *Cien Saude Colet.* 2017;22(8):2659-2669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28793080.

28. Cid-Silva P, Fernandez-Bargiela N, Margusino-Framinan L, et al. Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine. *Basic Clin Pharmacol Toxicol.* 2019;124(4):479-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30388308.

29. Patel K, Lindsey J, Angelidou K, Aldrovandi G, Palumbo P, Team IPS. Metabolic effects of initiating lopinavir/ritonavir-based regimens among young children. *AIDS.* 2018;32(16):2327-2336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30102656.

30. Taramasso L, Tatarelli P, Ricci E, et al. Improvement of lipid profile after switching from efavirenz or ritonavir-boosted protease inhibitors to rilpivirine or once-daily integrase inhibitors: results from a large observational cohort study (SCOLTA). *BMC Infect Dis.* 2018;18(1):357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30064371.

31. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation*. 2019;139(25):e1046-e1081. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30565953.

Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 16, 2019; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/Vomiting	All ARV drugs, but most notably RTV-boosted PIs	**Onset:** • Early **Presentation:** • Nausea and emesis, both of which may be associated with anorexia and/or abdominal pain	Varies by ARV agent; generally <15%	Unknown	Instruct patient to take PIs with food. Monitor for weight loss and ARV adherence.	Reassure patient that these adverse effects generally improve over time (usually in 6–8 weeks). Consider switching to ARV drugs with smaller tablet sizes (see Appendix A, Table 2). Provide supportive care. In extreme or persistent cases, use antiemetics or switch to another ARV regimen.
Diarrhea	All ARV drugs, but most notably RTV-boosted PIs	**Onset:** • Early **Presentation:** • More frequent bowel movements and stools that are generally soft	Varies by ARV agent; generally <15%	Unknown	Monitor for weight loss and dehydration.	In prolonged or severe cases, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea. Reassure patient that this adverse effect generally improves over time (usually in 6–8 weeks). Consider switching to another ARV regimen in persistent and severe cases. Treatment data in children are lacking; however, the following strategies may be useful when the ARV regimen cannot be changed: • Dietary modification • Using bulk-forming agents (e.g., psyllium) • Using antimotility agents (e.g., loperamide) • Using crofelemer, which is approved by the FDA to treat ART-associated diarrhea in adults aged ≥18 years; no pediatric data are available.

Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 16, 2019; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Pancreatitis	Rare, but may occur with NRTIs or RTV-boosted PIs	**Onset:** • Any time, usually after months of therapy **Presentation:** • Emesis, abdominal pain, elevated amylase and lipase levels (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<2% in a recent case series	Use of concomitant medications that are associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced HIV infection Previous episode of pancreatitis Alcohol use	Measure serum amylase and lipase concentrations if persistent abdominal pain develops.	Discontinue offending agent and **avoid reintroduction**. Manage symptoms of acute episodes. If pancreatitis is associated with hypertriglyceridemia, consider using interventions to lower TG levels.

Key: ART = antiretroviral therapy; ARV = antiretroviral; FDA = Food and Drug Administration; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole

References

1. Buck WC, Kabue MM, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children. *J Int AIDS Soc*. 2010;13:31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20691049.

2. Nachman SA, Chernoff M, Gona P, et al. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med*. 2009;163(2):164-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188649.

3. Hoffmann CJ, Fielding KL, Charalambous S, et al. Antiretroviral therapy using zidovudine, lamivudine, and efavirenz in South Africa: tolerability and clinical events. *AIDS*. 2008;22(1):67-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18090393.

4. Malan N, Su J, Mancini M, et al. Gastrointestinal tolerability and quality of life in antiretroviral-naive HIV-1-infected patients: data from the CASTLE study. *AIDS Care*. 2010;22(6):677-686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20467943.

5. Manfredi R, Calza L. HIV infection and the pancreas: risk factors and potential management guidelines. *Int J STD AIDS*. 2008;19(2):99-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18334062.

6. Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr*. 2012;59(3):274-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22126740.

7. Wegzyn CM, Fredrick LM, Stubbs RO, Woodward WC, Norton M. Diarrhea associated with lopinavir/ritonavir-based therapy: results of a meta-analysis of 1469

HIV-1-infected participants. *J Int Assoc Physicians AIDS Care (Chic).* 2012;11(4):252-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22544446.

8. Oumar AA, Diallo K, Dembele JP, et al. Adverse drug reactions to antiretroviral therapy: prospective study in children in sikasso (mali). *J Pediatr Pharmacol Ther.* 2012;17(4):382-388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23411444.

9. Wattanutchariya N, Sirisanthana V, Oberdorfer P. Effectiveness and safety of protease inhibitor-based regimens in HIV-infected Thai children failing first-line treatment. *HIV Med.* 2013;14(4):226-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23094820.

10. Van Dyke RB, Wang L, Williams PL, Pediatric AIDS Clinical Trials Group C Team. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19000014.

11. Clay PG, Crutchley RD. Noninfectious diarrhea in HIV seropositive individuals: a review of prevalence rates, etiology, and management in the era of combination antiretroviral therapy. *Infect Dis Ther*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25388760.

12. Szoke D, Ridolfo A, Valente C, Galli M, Panteghini M. Frequency of pancreatic hyperamylasemia in human immunodeficiency virus-positive patients in the highly active antiretroviral therapy era. *Am J Clin Pathol*. 2016;145(1):128-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26712880.

13. Castro JG, Chin-Beckford N. Crofelemer for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy. *Expert Rev Clin Pharmacol*. 2015;8(6):683-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26517110.

14. Dikman AE, Schonfeld E, Srisarajivakul NC, Poles MA. Human Immunodeficiency virus-associated diarrhea: still an issue in the era of antiretroviral therapy. *Dig Dis Sci*. 2015;60(8):2236-2245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25772777.

15. Logan C, Beadsworth MB, Beeching NJ. HIV and diarrhoea: what is new? *Curr Opin Infect Dis*. 2016;29(5):486-494. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27472290.